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Original Article

# EMPIRICAL FOLLOW-UP CRITIQUES OF STATIN DRUGS THROUGH OPTIMIZED COQ10 AND NIACIN DOSE COMBINATION TO OVERCOME GENETIC MUTATION OF CYTOCHROME P450 (CYP) 3A4

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***ABSTRACT***

***INTRODUCTION:*** *This work encompasses follow-up techniques to statin with coenzymes Q10 and Niacin so as to reduce the doses and frequency of Statin drugs. The genes synthesizing cytochrome P450 enzymes (CYP2D6, CYP3A4, and CYP3A5), a mitochondrial enzyme (GATM), an inflow transporter (SLCO1B1), and efflux transporters, which are all linked to elevated statin muscle concentrations (ABCB1 and ABCG2) lead to dangerous consequence of rhabdomyolysis. The CoQ10 and Niacin (Vitamin) is a rational bio-component, the follow-up therapy aid to terminate statin therapy.*

***METHODOLOGY:*** *The recommended 16 patients with all valid medical documentation were selected as per the criteria, those were already in the Statin treatment in a multi-specialty hospital. All physiological, Biochemistry, Pathological reports were assembled before entering to intervene therapy. Thereafter, the targeted drugs of CoQ10 & Niacin were administered to all patients individually as well as with combination. Both the groups administered doses for 15-30 days and resting time of 5-6 days respectively.*

***RESULT:*** *Data extracted from both (before & after the intervention) the therapy were comparatively analyzed by statistical tools, taking consideration of Correlation Regression values, Pearson's & Spearman's Correlation. The values are comparatively evaluated from Lipid Profiles of both therapies. All around the P-Value is < .00001. The result is significant at p < .05. ANOVA study between both the therapies was taken in contrast to evaluate the Triglyceride of LP which is a very essential parameter to analyze the Treatment variance. The f-ratio value is 2.25749. The p-value is 0.143424. The result is not significant at p < 0.05. A range difference in the triglyceride levels signifies the effectiveness of the treatment.*

***CONCLUSION:*** *Thus, slowly withdrawals of Statins dependency could be possible either by reducing the dose or replacing the total stains drug molecule from treatment profile which would work positively on max. Probability score.*

***KEYWORDS:*** *Chronic Statin Patients; Coq10 & Niacin Bio-Component; Rational Targeted Drugs; Comparative Statistical Reports & Higher Probability of Replacement.*

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## INTRODUCTION

For the most part, statin medicines appear to be safe to use. Patients who are suffering from or have several medical comorbidities, on the other hand, are at risk of negative side effects from long-term statin therapy **[1].** The most widely prescribed statin is atorvastatin, which is utilised by 99 percent of patients, with 63.5% of them experiencing adverse effects relating to respiratory, gastrointestinal, headache, rash, allergic responses, and some very rarely observed muscle-related side effects **[2].** There are two types of statins effects were found: mevalonate pathway inhibitors and dolichols. The former is used to block cholesterol synthesis, while the latter inhibits nuclear factor

kappa B. Statins have been discovered to have anti-inflammatory effects that aid in the reduction of cardiovascular risk **[3].** The review pointing on the genes synthesizing cytochrome P450 enzymes (CYP2D6, CYP3A4, and CYP3A5), a mitochondrial enzyme (GATM), an inflow transporter (SLCO1B1), and efflux transporters, which are all linked to elevated statin muscle concentrations (ABCB1 and ABCG2) **[4].** CoQ10 is an important antioxidant supplement that aids in slowing the progression of sickness that is under medical control. It's an endogenous lipid-soluble antioxidant that's found in all living things. COQ10 is the most well-known and widely utilised nutritional supplement. However, its specific dose, efficacy, and bioavailability have yet to be determined. The bioavailability of various delivery methods is also unknown. The OECD 428 approach is being used to investigate COQ10 topical absorption **[6].** COQ10 insufficiency is caused by biosynthesis failure caused by gene mutations, biosynthesis suppression induced by HMG co-enzyme A reductase inhibitors (statins), as well as age and cancer-like disorders **[7].** Several clinical trials on coenzyme Q10 looked into several novel COQ10 formulations for better medications with improved bioavailability and absorption **[8-16].** Most individuals obtain enough COQ10 from a healthy diet, but individuals who aren't able to keep their levels up can take supplements. It also aids in the enhancement of blood flow and the protection of blood vessels, as well as the reduction of plaque development in arteries **[9 -13].** COQ10 also aids in the reduction of apoptotic cell death caused by mitochondrial depolarization inhibition and cytochrome c release inhibition **[12-16].** It aids in the generation of ATP in the heart. Coenzyme Q10 doses imply that >2 mg/L is sufficient to achieve the therapeutic benefit or impact. COQ10 has extremely minimal negative side effects. ten) COQ10 supplementation is favourable to the brain and mitochondrial concentrations in the brain **[18].** COQ10 is also effective against UVA-mediated oxidative damage in humans, according to the study**.** Preclinical investigations indicated that supplementing COQ10 with a dose of atorvastatin is advantageous in hypercholesterolemic rats, and that this therapeutic effect can also be tried in patients who take statins and have high cholesterol **[13].** Niacin's effects on alternating HDL levels. It has the ability to control aberrant lipoproteins as well as lower cardiovascular events. Because of its tolerability difficulties, niacin's use is restricted. It's only accessible in a few different formulations, and those formulations have their own set of side effects **[20-22].** Niacin requires additional research into dose, follow-up, and regimen modifications, among other things. Further, more effective niacin counselling is needed to enhance patient adherence use of important cardioprotective drug **[23].** Furthermore, research such as RCTs and clinical trials are required to determine the drug's precise safety, effectiveness, and dose.

## METHODOLOGY

The total protocol was dependent upon patient categories, patient size, patient’s consent, hospital facilities, medical team support, quality of analytical instruments, availability of chemicals and raw materials. So, there were two parts, one was the laboratory portion and the other was the clinical study. So, the entire procedure scheme was stepwise oriented as below.

### Selection of Patients

The patients were categorized as per clinical criteria. Both diabetic and /or Hyperglycemic and cardiovascular patients are selected. These patients further sub-categorize as per demography, life-style and socio-economic status. The patient's angiographic image was selected normal and devoid from the risk of angioplasty of CABG chances.

**Patients Size**

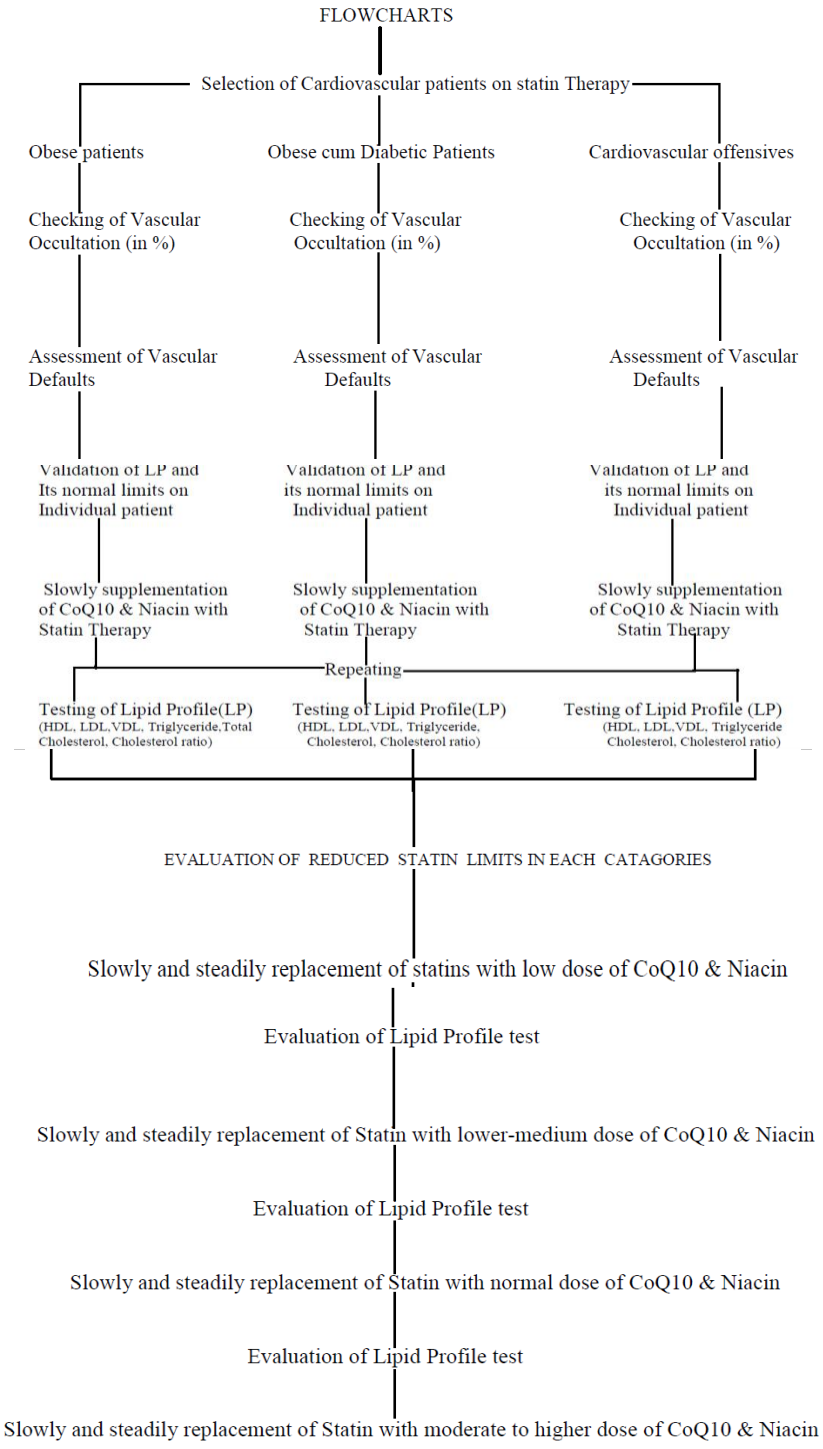
This was an interventional study and laboratory bio-fluid specimen analysis was collected consecutively after validation of administrative basic drugs and supportive medicine. So, this study was targeted to engage 20 required patients, which satisfies the inclusion clinical criteria.

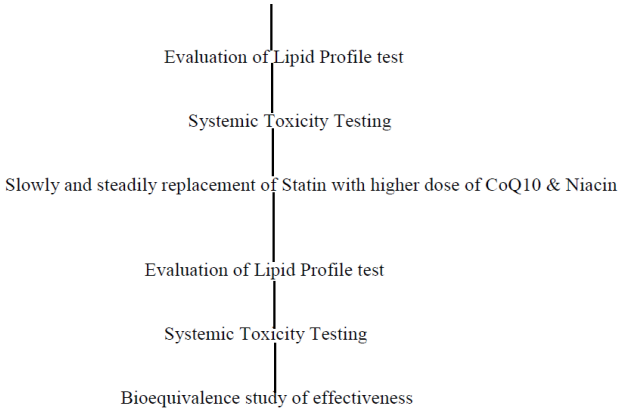
**Procedures**

The case study was started in Innocent Heart Multi-specialist Hospital, but only 16 patients were selected as per the criteria. The fundamental drug was anti lipidemic drugs Statin like Atorvastatin, Simvastatin and Rosuvastatin which are running as per the ongoing routine therapy as usual. Our motive is not to do any changes with the usual drugs/dosage/doses but just in cooperation with clinicians we are planning to include the targeted drugs i.e., CoQ10 & Niacin (already rational drugs which doctors prescribe for cardiovascular patients).

- The demographic details, medication history, medical history, Pathological & Biochemistry reports and physiological states were scrutinized for all 16 patients. Mostly focus was depicted on the Physiological parameters and Pathological- Biochemistry reports like Lipid Profile, BP, ECG etc. And before going through the experimental parts, all these parameters have been reported. The expectation was to assess whether the additional use of the targeted drugs could change these parameters towards positive or negative path of targeted study?
- Test of inclusion of CoQ10 & Niacin was carried out for months for these chronic 16 targeted patients, as per individual drug one –by- one and in combination. The individual both drugs were administered for 15-30 days separately along with usual treatment of Statin, as well as combination (CoQ10 & Niacin) of targeted drugs for the same 15-30 days. Each drug or individual drug treatment when finished after 15-30 days, there is a resting period of 4-5 days, such that the total drugs component on body tissue gets nullified. After that combination of drugs treatment was started the same way for 15-30 days, thereafter 4-5 days of resting periods.
- Simultaneously, at each end of this treatment, the Pathological- Biochemistry reports like Lipid Profile, BP, ECG etc were evaluated.
- After getting both types of reports (of steps a & c), it was compared and the data evolved was statistically confined to confirm the changes coming in a positive way or deviated in negative turns?

## DESIGNED PROTOCOL






## RESULTS & DISCUSSIONS

### Total Cholesterol Level Assessment

The total Cholesterol level was analyzed with ongoing treatment and comparatively with the intervention of CoQ10 + niacin tablets. So, calibrated histograms show that after intervention of therapy with drug inclusion, it shows remarkable depletion of the Total cholesterol, **Figure-1.**

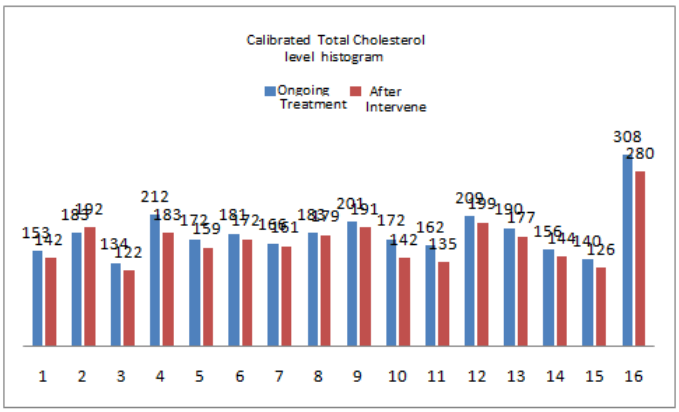



**Figure 1: Total Cholesterol Level Histograms.**

### Evaluation of HDL Ievel

HDL has a great importance on study, where before intervention therapies the HDL level evaluated on average was higher in all 16 patients. The use of drug intervention with Co Q10 + Niacin with the usual therapy increased the good cholesterol. The same has been illustrated in the Histograms, **Figure-2.**

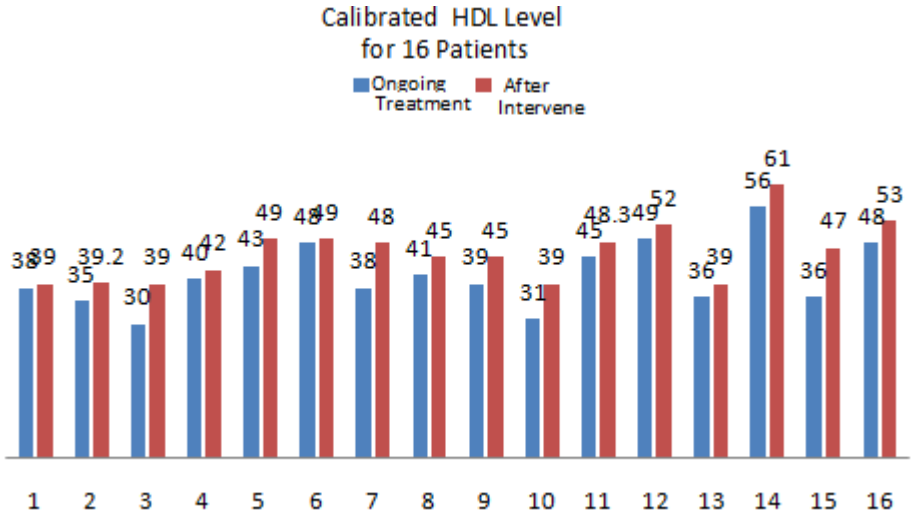



**Figure 2: Comparative HDL Values of 16 Patients.**

For HDL, the correlation coefficients are statistically traced, such as Pearson's Correlation coefficients and Spearman Correlation coefficient. Pearson's Correlation coefficient reflects R= 0.8989 with $R^2$ = 0.808. The P-Value is < 0.00001. The result is significant at p< 0.05. The HDL values statistical evaluation: Pearson's Correlation Coefficient.

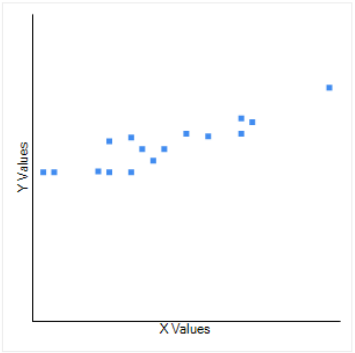



**Figure 3: Correlation Representation of HDL Values among with and without Intervening Drugs as X & Y Variables Respectively. The aluve of R is 0.8989.**

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This is a strong positive correlation, which means that high X variable scores go with high Y variable scores (and vice versa). The P-Value is < .00001. The result is significant at p < .05. The value of $R^2$, the coefficient of determination, is 0.808.

Spearman Correlation coefficient, $r_s$ = 0.87809, $p$ (2-tailed) = 1E-05. By normal standards, the association between the two variables would be considered statistically significant.

**Linear Regression for VLDL Level Evaluation**

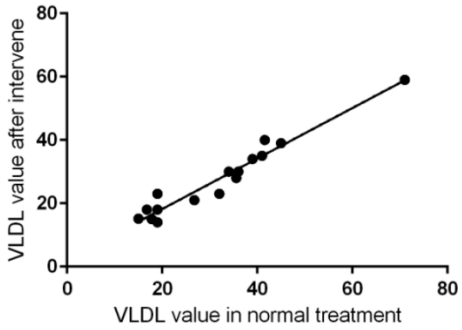



**Figure 4: Linear Regression Correlation of VLDL Level among Both Therapy, Values among with and without Drugs.**

| Best-Fit Values | 95% Confidence Intervals | Is Slope Significantly Non-Zero? |
|---|---|---|
| Slope0.7970 ± 0.04997<br>Y-intercept2.302 ± 1.739<br>X-intercept-2.888<br>1/Slope1.255 | Slope0.6898 to 0.9042<br>Y-intercept-1.427 to 6.031<br>X-intercept-8.650 to 1.595<br>Goodness of Fit<br>R square0.9478<br>Sy.x2.827 | F254.4<br>DFn,DFd1,14<br>P Value< 0.0001<br>Deviation from horizontal? Significant<br>Data<br>Number of XY pairs16<br>EquationY = 0.7970*X + 2.302 |

The VLDL level evaluation was carried off between both therapies, before and after interventions. It was discovered that CoQ10 + Niacin lowers the VLDL level on all 6 patients except one. And the linear regression coefficient is significant and the $R^2$ = 0.7970*X + 2.302.

**Evaluation of LDL Level**

Corresponding to VLDL level, LDL level also moves at the same pace on comparative studies of the treatment before and after intervention with CoQ10 + Niacin. Here, the linear regression coefficient was traced off between two variables of therapy. This is showing strong positive correlations. Where, R = 0.8845; p-value of < 0.00001. Thus, the variation of the therapy runs with significant value parallel to each other.

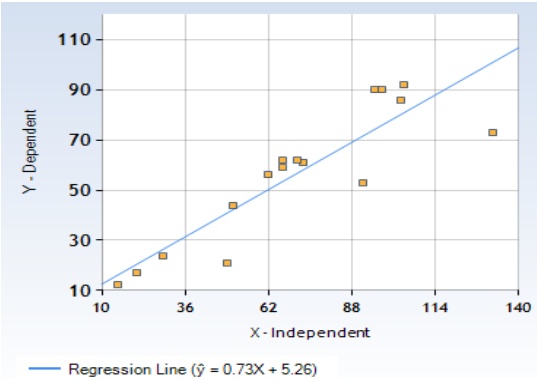



**Figure 5: Linear Regression Correlation of LDL Level among Both Therapy, Values among with and without Drugs.**

The value of **R** is 0.8845. This is a strong positive correlation, which means that high X variable scores go with high Y variable scores (and vice versa). The value of $\mathbf{R^2}$, the coefficient of determination, is 0.7823. The P-Value is <0.00001. The result is significant at p< 0.05.

**Evaluation of Triglyceride**

The Triglycerides are the game changing element to prove the effects of new intervention therapy compared to the ongoing existing therapy. The calibrated histogram is remarkably showing the variations in the triglyceride level after giving the CoQ10 + Niacin as a new intervention therapy, figure-

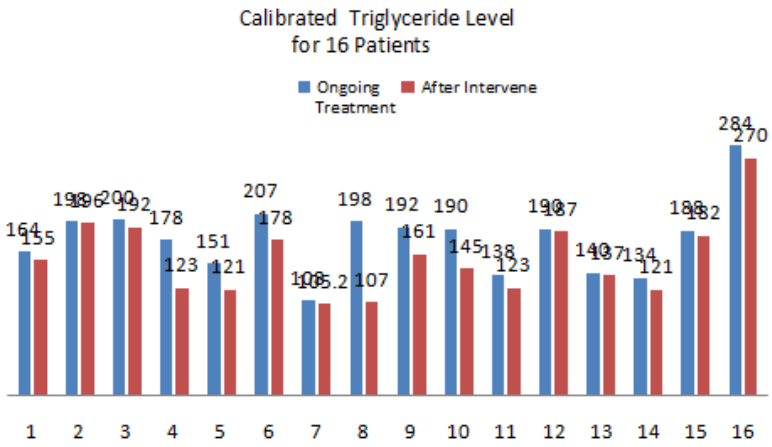
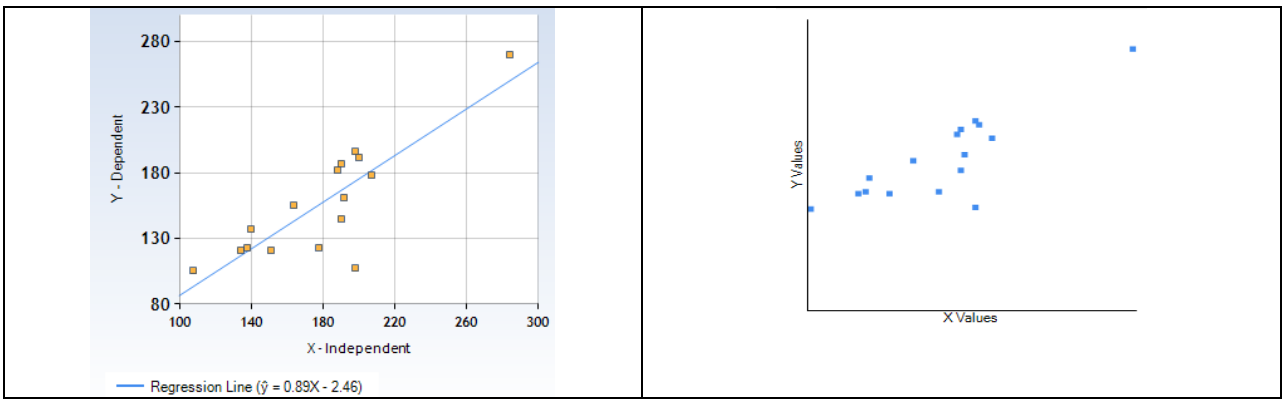



**Figure 6: Comparative Triglyceride Level under the 16 Patients.**

The Linear regression correlation, Spearman's and Pearson's correlation coefficients were traced out to get the values for significance. This is showing a strong positive correlation among both therapies.




Pearson's Correlation coefficient results: The value of R is 0.8338. This is a strong positive correlation, which means that high X variable scores go with high Y variable scores (and vice versa). The value of $R^2$, the coefficient of determination, is 0.6952. The P-Value is 0.00006. The result is significant at $p < 0.05$.

**ANOVA Study for Triglyceride**

ANOVA study between both the therapies was taken on contrast to evaluate the Triglyceride of LP which is very essential parameter to analyze the Treatment variance. A range difference in the triglyceride levels signifies the effectiveness of the

treatment. The f-ratio value is 2.25749. The p-value is 0.143424. The result is not significant at $p < 0.05$. The not significant values means more variations in inter & intra- treatment accesses. It's natural to get intra-treatment variance because the large variance of random selection of patients demography was selected. The wide inter-treatment variance is mostly reflected here because this triglyceride level is showing the wide difference in their values which is the best impact of positive result.

## CONCLUSIONS

Ongoing through the total lipid profile (LP) variations of ongoing and intervene therapy, it was discovered that the VLDL, LDL, Total Cholesterol, Cholesterol ratios, Triglyceride all are promoting depletion profile of the LP, except the HDL (Good cholesterol). The comparative study of statins alone and in combination therapy with Co Q10 + Niacin would finally clear the picture that the correlations of the variation are more significant. Thus, slowly withdrawals of statins dependency either by reducing the dose or replacing the total drug molecule stains from treatment profile will work positively on max. Probability score.

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